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1: Science. 2003 Apr 25;300(5619):644-7. Epub 2003 Apr 10.

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DAF-16 target genes that control C. elegans life-span and metabolism.

Lee SS, Kennedy S, Tolonen AC, Ruvkun G.

Department of Molecular Biology, Massachusetts General Hospital, Department of Genetics, Harvard Medical School, 50 Blossom Street, Boston, MA 02114, USA.

Signaling from the DAF-2/insulin receptor to the DAF-16/FOXO transcription factor controls longevity, metabolism, and development in disparate phyla. To identify genes that mediate the conserved biological outputs of daf-2/insulin-like signaling, we used comparative genomics to identify 17 orthologous genes from Caenorhabditis and Drosophila, each of which bears a DAF-16 binding site in the promoter region. One-third of these DAF-16 downstream candidate genes were regulated by daf-2/insulin-like signaling in C. elegans, and RNA interference inactivation of the candidates showed that many of these genes mediate distinct aspects of daf-16 function, including longevity, metabolism, and development.

PMID: 12690206 [PubMed - indexed for MEDLINE]

1: Curr Biol. 2001 Dec 11;11(24):1950-7.

Related Articles, Links

Regulation of C. elegans DAF-16 and its human ortholog FKHRL1 by the daf-2 insulin-like signaling pathway.

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C. elegans insulin-like signaling regulates metabolism, development, and life span. This signaling pathway negatively regulates the activity of the forkhead transcription factor DAF-16. daf-16 encodes multiple isoforms that are expressed in distinct tissue types and are probable orthologs of human FKHRL1, FKHR, and AFX. We show that human FKHRL1 can partially replace DAF-16, proving the orthology. In mammalian cells, insulin and insulin-like growth factor signaling activate AKT/PKB kinase to negatively regulate the nuclear localization of DAF-16 homologs (reviewed in). We show that the absence of AKT consensus sites on DAF-16 is sufficient to cause dauer arrest in daf-2(+) animals, proving that daf-16 is the major output of insulin signaling in C. elegans. FKHR, FKRHL1, and AFX may similarly be the major outputs of mammalian insulin signaling. daf-2 insulin signaling, via AKT kinases, negatively regulates DAF-16 by controlling its nuclear localization. Surprisingly, we find that daf-7 TGF-beta signaling also regulates DAF-16 nuclear localization specifically at the time when the animal makes the commitment between diapause and reproductive development. daf-16 function is supported by the combined action of two distinct promoter/enhancer elements, whereas the coding sequences of two major DAF-16 isoforms are interchangeable. Together, these observations suggest that the combined effects of transcriptional and posttranslational regulation of daf-16 transduce insulin-like signals in C. elegans and perhaps more generally.

PMID: 11747821 [PubMed - indexed for MEDLINE]

1: Genetics. 1994 May;137(1):107-20.

Related Articles, Links

daf-2, daf-16 and daf-23: genetically interacting genes controlling Dauer formation in Caenorhabditis elegans.

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Under conditions of high population density and low food, Caenorhabditis elegans forms an alternative third larval stage, called the dauer stage, which is resistant to desiccation and harsh environments. Genetic analysis of some dauer constitutive (Daf-c) and dauer defective (Daf-d) mutants has revealed a complex pathway that is likely to function in particular neurons and/or responding tissues. Here we analyze the genetic interactions between three genes which comprise a branch of the dauer formation pathway that acts in parallel to or downstream of the other branches of the pathway, the Daf-c genes daf-2 and daf-23 and the Daf-d gene daf-16. Unlike mutations in other Daf-c genes, mutations in both daf-2 and daf-23 cause non-conditional arrest at the dauer stage. Our epistasis analysis suggests that daf-2 and daf-23 are functioning at a similar point in the dauer pathway. First, mutations in daf-2 and daf-23 are epistatic to mutations in the same set of Daf-d genes. Second, daf-2 and daf-23 mutants are suppressed by mutations in daf-16. Mutations in daf-16 do not suppress any of the other Daf-c mutants as efficiently as they suppress daf-2 and daf-23 mutants. Third, double mutants between either daf-2 or daf-23 and several other daf-d mutants exhibit an unusual interaction. Based on these results, we present a model for the function of daf-2, daf-23 and daf-16 in dauer formation.

PMID: 8056303 [PubMed - indexed for MEDLINE]

1: Proc Natl Acad Sci U S A. 2000 Sep 12;97(19):10412-7.

Related Articles, Links

DAF-16 recruits the CREB-binding protein coactivator complex to the insulin-like growth factor binding protein 1 promoter in HepG2 cells.

Nasrin N, Ogg S, Cahill CM, Biggs W, Nui S, Dore J, Calvo D, Shi Y, Ruvkun G, Alexander-Bridges MC.

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Insulin negatively regulates expression of the insulin-like growth factor binding protein 1 (IGFBP-1) gene by means of an insulin-responsive element (IRE) that also contributes to glucocorticoid stimulation of this gene. We find that the Caenorhabditis elegans protein DAF-16 binds the IGFBP-1 small middle dotIRE with specificity similar to that of the forkhead (FKH) factor(s) that act both to enhance glucocorticoid responsiveness and to mediate the negative effect of insulin at this site. In HepG2 cells, DAF-16 and its mammalian homologs, FKHR, FKHRL1, and AFX, activate transcription through the IGFBP-1.IRE; this effect is inhibited by the viral oncoprotein E1A, but not by mutants of E1A that fail to interact with the coactivator p300/CREB-binding protein (CBP). We show that DAF-16 and FKHR can interact with both the KIX and E1A/SRC interaction domains of p300/CBP, as well as the steroid receptor coactivator (SRC). A C-terminal deletion mutant of DAF-16 that is nonfunctional in C. elegans fails to bind the KIX domain of CBP, fails to activate transcription through the IGFBP-1.IRE, and inhibits activation of the IGFBP-1 promoter by glucocorticoids. Thus, the interaction of DAF-16 homologs with the KIX domain of CBP is essential to basal and glucocorticoid-stimulated transactivation. Although AFX interacts with the KIX domain of CBP, it does not interact with SRC and does not respond to glucocorticoids or insulin. Thus, we conclude that DAF-16 and FKHR act as accessory factors to the glucocorticoid response, by recruiting the p300/CBP/SRC coactivator complex to an FKH factor site in the IGFBP-1 promoter, which allows the cell to integrate the effects of glucocorticoids and insulin on genes that carry this site.

PMID: 10973497 [PubMed - indexed for MEDLINE]

1: Biochem J. 2000 Jul 15;349(Pt 2):629-34.

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Biochem J

Identification of the differential distribution patterns of mRNAs and consensus binding sequences for mouse DAF-16 homologues.

Furuyama T, Nakazawa T, Nakano I, Mori N.

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daf-16 is a forkhead-type transcription factor, functioning downstream of insulin-like signals, and is known to be critical to the regulation of life span in Caenorhabditis elegans. Mammalian DAF-16 homologues include AFX, FKHR and FKHRL1, which contain a conserved forkhead domain and three putative phosphorylation sites for the Ser/Thr kinase Akt/protein kinase B (PKB), as well as for DAF-16. To assess the function of the homologues, we examined tissue distribution patterns of mRNAs for DAF-16 homologues in mice. In the embryos, expressions of AFX, FKHR and FKHRL1 mRNAs were complementary to each other and were highest in muscle, adipose tissue and embryonic liver. The characteristic expression pattern remained in the adult, except that signals of FKHRL1 became evident in more tissues, including the brain. In order to clarify whether each DAF-16 homologue had different target genes, we determined the consensus sequences for the binding of DAF-16 and the mouse homologues. The binding sequences for all four proteins shared a core sequence, TTGTTTAC, daf-16 family protein-binding element (DBE) binding protein. However, electrophoretic mobility shift assay showed that the binding affinity of DAF-16 homologues to the core sequence was stronger than that to the insulin-responsive element in the insulin-like growth factor binding protein-1 promoter region, which has been identified as a binding sequence for them. We identified one copy of the DBE upstream of the first exon of sod-3 by searching the genomic database of C. elegans. Taken together, DAF-16 homologues can fundamentally regulate the common target genes in insulin-responsive tissues and the specificity to target genes of each protein is partially determined by the differences in their expression patterns.

PMID: 10880363 [PubMed - indexed for MEDLINE]

1: Nature. 1997 Oct 30;389(6654):994-9.

nature

The Fork head transcription factor DAF-16 transduces insulin-like metabolic and longevity signals in C. elegans.

Ogg S, Paradis S, Gottlieb S, Patterson GI, Lee L, Tissenbaum HA, Ruvkun G.

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In mammals, insulin signalling regulates glucose transport together with the expression and activity of various metabolic enzymes. In the nematode Caenorhabditis elegans, a related pathway regulates metabolism, development and longevity. Wild-type animals enter the developmentally arrested dauer stage in response to high levels of a secreted pheromone, accumulating large amounts of fat in their intestines and hypodermis. Mutants in DAF-2 (a homologue of the mammalian insulin receptor) and AGE-1 (a homologue of the catalytic subunit of mammalian phosphatidylinositol 3-OH kinase) arrest development at the dauer stage. Moreover, animals bearing weak or temperature-sensitive mutations in daf-2 and age-1 can develop reproductively, but nevertheless show increased energy storage and longevity. Here we show that null mutations in daf-16 suppress the effects of mutations in daf-2 or age-1; lack of daf-16 bypasses the need for this insulin receptor-like signalling pathway. The principal role of DAF-2/AGE-1 signalling is thus to antagonize DAF-16. daf-16 is widely expressed and encodes three members of the Fork head family of transcription factors. The DAF-2 pathway acts synergistically with the pathway activated by a nematode TGF-beta-type signal, DAF-7, suggesting that DAF-16 cooperates with nematode SMAD proteins in regulating the transcription of key metabolic and developmental control genes. The probable human orthologues of DAF-16, FKHR and AFX, may also act downstream of insulin signalling and cooperate with TGF-beta effectors in mediating metabolic regulation. These genes may be dysregulated in diabetes.

PMID: 9353126 [PubMed - indexed for MEDLINE]